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Iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism in a community-based cohort

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Abstract

Recent data suggest iodinated contrast media (ICM) exposure is associated with increased risk of incident hyperthyroidism among patients receiving care from two tertiary care medical centers. We sought to confirm and generalize these findings by conducting a case-control study among a broadly-representative community-based cohort of patients receiving care within Harvard Vanguard Medical Associates from 1996 to 2012. Incident hyperthyroid and hypothyroid cases were defined by change in thyrotropin (TSH) from normal (at baseline), to low or high (at follow-up), respectively. In parallel analyses, hyper- and hypothyroid cases were matched to euthyroid controls using incidence density sampling, and ICM exposure was ascertained using claims data. Secondary analyses examined associations with incident overt hyperthyroidism and overt hypothyroidism (follow-up TSH≤0.1 mIU/L and TSH>10 mIU/L, respectively). We observed that ICM exposure was associated with increased risk of incident hyperthyroidism [odds ratio, 1.61 (95% CI) 1.27-2.04], incident overt hyperthyroidism [odds ratio, 1.62 (95% CI) 1.08-2.43], and incident overt hypothyroidism [odds ratio 2.01 (95% CI) 1.25-3.23]. These data confirm that ICM exposure is associated with increased risk of incident thyroid functional disease in a community-based cohort of patients in an iodine-sufficient region.

Introduction

Iodine is an essential element for thyroid hormone synthesis.[1,2] However, in some patients exposure to supraphysiologic levels inhibits thyroid hormone synthesis, resulting in hypothyroidism. Conversely, in other patients high iodide levels provide excess substrate for unregulated thyroid hormone formation, resulting in hyperthyroidism (Jöd Basedow phenomenon). Such phenomena have been observed in response to a variety of exposures including those that confer as little as 300 mcg of iodide.[2,3]

Iodinated contrast media (ICM) exposure has risen over the past two decades in parallel with increased utilization of contrast-based computed tomography (CT) and cardiac angiography.[4] ICM represents a significant iodine load: a single dose contains 13,500 μg of free iodide, as well as 15-60 g of bound iodine that may be liberated to free iodide following administration.[4,5] The implied iodide load is 90-to-several-hundred-thousand-fold the daily recommended intake for adults (150 mcg).

Recently, we reported that ICM was independently associated with incident hyperthyroidism and incident overt hyperthyroidism.[6] Patients in that study had care centered at one of two tertiary care centers in the Partners Health Care system. Given that these patients may differ from the general population in terms of socio-demographics and overall health status that may have bearing on the risk of thyroid functional disease, we sought to validate findings in a more broadly representative population. This study therefore was designed to estimate the association between ICM receipt and incident thyroid functional disease among a contemporary cohort of patients cared for by Harvard Vanguard Medical Associates (HVMA), a large community-based multispecialty group in the New England area.

Materials and Methods

Study cohort

The study protocol was approved by the Partners HealthCare Institutional Review Board. We conducted a nested case-control study using administrative data from HVMA, a large nonprofit multispecialty group practice in New England providing care to 325,000 patients with >3 million ambulatory visits on an annual basis.[7] HVMA has an integrated electronic medical record system with comprehensive capture of longitudinal data on socio-demographics, diagnostic and procedural codes, laboratory results, prescription dispensation, ambulatory encounters, and vital status, and has been employed in numerous health services and epidemiologic research studies.[8]

Patients were included provided that they were age ≥18 years old and met the following criteria: i. Had at least one *normal* TSH level measured between January 1, 1996 and August 30, 2012 (designated as *baseline*); ii. Prior to baseline, had no diagnosis of thyroid functional disorder as ascertained by International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes; iii. Prior to baseline, had no laboratory evidence of abnormal thyroid function [thyrotropin (TSH), free thyroxine (FT4), free thyroxine index (FT4I), or total thyroxine (TT4) outside the laboratory assay ref-

erent range]; iv. Prior to or at baseline, did not use thyroid hormone supplements or thyroid suppressive medication; v. Prior to baseline, had no radioactive iodine ablation or surgical thyroidectomy as ascertained by Current Procedural Terminology or ICD-9 procedural codes; vi. Subsequent to baseline, had a TSH measured within 2 weeks to 2 years (designated as *follow-up*). Criteria 1 to 5 were designated in order to limit consideration to cases of *incident* functional disease.

Case and control designation

Given that the baseline TSH was normal for all subjects, case status was ascribed according to the follow-up TSH level. Incident hyperthyroidism was defined by follow-up TSH < assay referent range and incident hypothyroidism as follow-up TSH > assay referent range. Euthyroid controls were designated as those in whom the TSH remained within assay referent range at follow-up. Due to sparsity of measurement, TT4, FT4, and FT4I levels were not included in the case definition. In secondary analyses, we examined cases of incident overt hyperthyroidism (follow-up TSH≤0.1 mIU/L) and incident overt hypothyroidism (follow-up TSH>10 mIU/L) using cut-offs associated with clinically significant outcomes.[9,10] Sensitivity analyses were conducted which excluded patients with prior exposure to lithium or amiodarone or other iodine-containing medications.

Separate analogous analyses were conduct-ed for incident hyperthyroidism, incident overt hyperthyroidism, incident hypothyroidism, and incident overt hypothyroidism. Controls were sampled using an incidence density sampling paradigm in which patients were eligible to contribute ≥1 patient-time interval(s) to the analyses, provided that each interval met the inclusion/exclusion criteria outlined above. At each time point at which a case was identified, up to four controls were randomly selected. Controls were matched to cases on the basis of: sex, age (±10 years), race/ethnicity (white versus nonwhite), follow-up TSH measurement date (±2 years), interval between baseline and follow-up TSH date (≤180, 181-360, 361-540, 541-720 days), estimated glomerular filtration rate (eGFR, derived from the Chronic Kidney Disease Epidemiology Collaboration study equation using the most proximate creatinine ≤1 year preceding baseline TSH measurement if available; <45, 46-59, ≥60 mL/min/1.73 m², or missing) in order to reduce the risk of confounding.[11]

Exposure ascertainment

For each patient-time interval (cases and controls), ICM exposure was defined as ICM exposure between the dates of baseline and follow-up TSH measurements. ICM exposure was derived from ICD-9 and CPT procedural claims codes for contrast-enhanced CT, cardiac catheterization, or peripheral angiography.

Statistical analyses

The association between ICM exposure and outcome was estimated using conditional logistic regression models grouped on matched assignment. P-values <0.05 were considered statistically significant. Analyses were performed using Stata MP 10.1 (StataCorp, College Station, TX).

Results

Source cohort description

Overall, the source cohort was comprised of 349,869 qualifying patient intervals, among which 3822 incident hyperthyroid cases, 7001 incident hypothyroid, and 339,046 eligible euthyroid controls were identified. ICM was administered during 11,110 (3.2%) of the eligible patient intervals. ICM was administered in the context of a CT scan during 10,343 intervals (3.0%), cardiac catheterization or peripheral angiography during 822 intervals (0.2%), and both CT scan and cardiac catheterization/peripheral angiography during 55 intervals (0.01%).

Association between iodinated contrast media exposure and hyperthyroidism

Of 3822 eligible cases of incident hyperthyroidism, 3821 cases were matched to 15,282

Table 1. Comparison of baseline characteristics between incident hyperthyroid and hypothyroid cases versus controls in the source cohort and the matched analytical cohort.

Characteristics	Source cohort						Matched cohort	
	Unmatched controls (n=339,046) (n=3822)	Unmatched hyperthyroid cases	Unmatched controls (n=339,046)	Unmatched hypothyroid cases	Matched controls (n=15,282) (n=3821)	Matched hyperthyroid cases	Matched controls (n=27,981)	Matched hypothyroid cases (n=7000)
Age (mean±SD)	52.2±16.4	48.4±16.2	52.2±16.4	55.4±17.5	48.5±15.6	48.4±16.2	55.1±16.7	55.4±17.5
Female n. (%)	233,512 (68.9)	2985 (78.1)	233,512 (68.9)	4971 (71.0)	11,940 (78.1)	2985 (78.1)	19,880 (71.1)	4971 (71.0)
White n. (%)	236,143 (69.7)	2284 (59.8)	236,143 (69.7)	5389 (77.0)	9136 (59.8)	2284 (59.8)	21,553 (77.0)	5389 (77.0)
Renal function n. (%)*								
≥60	162,187 (47.8)	1501 (39.3)	162,187 (47.8)	3034 (43.3)	6004 (39.3)	1501 (39.3)	12,136 (43.4)	3034 (43.3)
45-59	20,150 (5.9)	212 (5.6)	20,150 (5.9)	551 (7.9)	842 (5.5)	211 (5.5)	2198 (7.9)	551 (7.9)
<45	9539 (2.8)	105 (2.8)	9539 (2.8)	370 (5.3)	420 (2.8)	105 (2.8)	1463 (5.2)	369 (5.3)
Missing	147,170 (43.4)	2004 (52.4)	147,170 (43.4)	3046 (43.5)	8016 (52.5)	2004 (52.5)	12,184 (43.5)	3046 (43.5)
Interval baseline/ follow-up TSH	370	309	370	365	316	309	366	365
Median (IQR)	(219-478)	(147-451)	(219,478)	(200-478)	(152-448)	(147-451)	(201-471)	(200-478)
Era n. (%)**								
1990-1994	16,344 (4.8)	439 (11.5)	16,344 (4.8)	465 (6.6)	1740 (11.4)	439 (11.5)	1640 (5.9)	464 (6.6)
1995-1999	53,153 (15.7)	876 (22.9)	53,153 (15.7)	1277 (18.2)	3548 (23.2)	876 (22.9)	5127 (18.3)	1277 (18.2)
2000-2004	88,540 (26.1)	1322 (34.6)	88,540 (26.1)	1260 (18.0)	5096 (33.4)	1321 (34.6)	5249 (18.8)	1260 (18.0)
2005-2009	93,020 (27.4)	753 (19.7)	93,020 (27.4)	2066 (29.5)	3145 (20.6)	753 (19.7)	7715 (27.6)	2066 (29.5)
2010-2012	87,989 (26.0)	432 (11.3)	87,989 (26.0)	1933 (27.6)	1753 (11.5)	432 (11.3)	8250 (29.5)	1933 (27.6)
Contrast exposure n. (%)	10,754 (3.2)	103 (2.7)	10,754 (3.2)	253 (3.6)	265 (1.7)	103 (2.7)	999 (3.6)	253 (3.6)

*mL/min/1.73m² **based on follow up TSH date; TSH, thyrotropin; IQR, interquartile.

controls. Incident hyperthyroid cases and controls were well-balanced on baseline covariates (Table 1). In matched analysis, there was a significant association between ICM exposure and incident hyperthyroidism (Figure 1). On secondary analysis, there was a significant association between ICM exposure and incident overt hyperthyroidism in 1122 cases matched to 4488 controls (Figure 1).

Results were qualitatively similar in sensitivity analyses restricted to cases and controls without prior exposure to lithium or amiodarone or other iodine-containing medications. The adjusted ORs (95% CIs) for ICM exposure were 1.65 (1.30-2.10; P<0.001) for incident hyperthyroidism and 1.52 (1.00-2.32; P=0.05) for incident overt hyperthyroidism.

Association between iodinated contrast media exposure and hypothyroidism

Of 7001 eligible cases of incident hyperthyroidism, 7000 cases were matched to 27,981 controls. Hypothyroid cases and controls were well-balanced on baseline covariates (Table 1). In matched analysis, we did not observe a significant association between ICM exposure and incident hypothyroidism (Figure 1). On secondary analysis, we observed a significant association between ICM exposure and incident overt hypothyroidism among 812 cases matched to 3248 controls: OR 2.01 (95% CI) 1.25-3.23; P<0.001 (Figure 1).

Results were qualitatively similar in sensitivity analyses limited to cases and controls without prior exposure to lithium or amiodarone or other iodine-containing medications. The adjusted ORs (95% CIs) for ICM exposure were 1.00 (0.86-1.15; P>0.9) for incident hypothyroidism and 2.53 (1.51-4.24; P<0.001) for incident overt hypothyroidism.

Discussion

In this study, we observed that there was a significant association between ICM exposure and incident hyperthyroidism within a community-based cohort of ambulatory patients in the New England area. Under normal conditions, free iodide is an essential element for thyroid hormone synthesis.[1,2] However, it has long been recognized that acute or chronic exposure to excess iodine from non-ICM sources (e.g., medications, disinfectants, diet) may result in thyrotoxicosis in some patients.[2,12] Iodine-induced hyperthyroidism (Jöd Basedow phenomenon) has typically been described in patients with latent nodular or diffuse goiter or Graves' disease residing in areas of iodine deficiency who remain clinically euthyroid until iodine repletion.[1,13,14] However, iodine-induced hyperthyroidism has also been observed in patients without pre-existing thyroid disease residing in iodine-replete regions.[15] Using data from the Partners

HealthCare system, we recently reported the first controlled study of ICM-associated thyrotoxicosis amongst 178 and 76 cases with incident hypothyroidism and incident overt hyperthyroidism, respectively, in an iodine-sufficient region in Boston.[6] However, given that this preliminary study considered patients whose care was centered at tertiary centers and who were also sociodemographically homogenous, generalizability of findings to community-based populations, particularly those with greater racial/ethnic diversity, had been uncertain. We thus sought to examine these associations within a large, community-based cohort whose health status was more representative of the broader population. We again observed a significant association between ICM exposure with incident hyperthyroidism and overt hyperthyroidism, corroborating earlier findings. These collective data bear great clinical relevance given the known adverse effects of hyperthyroidism on multiple organ systems (i.e., bone, neuropsychiatric)[16] particularly the cardiovascular system (e.g., atrial fibrillation, high-output heart failure, angina, and possibly greater cardiovascular mortality).[17,18] Although untested, it has been suggested that prophylactic treatment with methimazole or perchlorate may be warranted in high-risk patients in advance of anticipated iodide exposure such as elective ICM-based procedures;[2,19,20] further studies are needed to evaluate the safety and effectiveness of this approach.

Consistent with prior findings, we also observed that ICM was associated with incident overt hypothyroidism. Although the mechanism of iodine-induced hypothyroidism (failure to escape from the acute Wolff-Chaikoff effect) has not been fully elucidated, it has been presumed to be due to i) iodine-induced inhibition of the sodium-iodide transporter, or ii) generation of iodolipids and iodolactones that inhibit thyroid peroxidase, and is typically observed in iodine-replete regions.[20-22] Given the potential long-term effects of untreated hypothyroidism (i.e., diastolic hypertension, dyslipidemia, atherosclerosis, and impaired cardiac contractility and relaxation),[23] patients who may be unable to tolerate hypothyroidism due to underlying cardiovascular disease may benefit from thyroid function monitoring following ICM exposure.[20]

Strengths of our study include the examination of a large number of patients with laboratory data and procedures captured within an integrated electronic health care record system; use of rigorous case criteria in order to establish incident hyper- and hypothyroidism; and adjustment for multiple confounders by matching. However, several limitations of our study bear mention. First, this study examined patients from an iodine-sufficient region, and therefore results may not be generalizable to
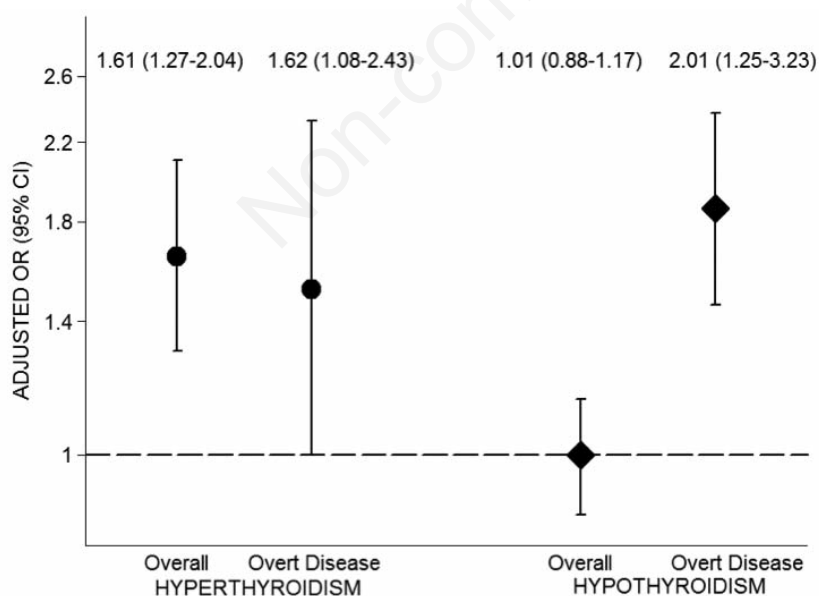

Figure 1. Associations between iodinated contrast media exposure with incident hyperthyroidism, incident overt hyperthyroidism, incident hypothyroidism, and incident overt hypothyroidism. Each was estimated in separate parallel analyses, matched for age, sex, race/ethnicity, baseline renal function, follow-up thyrotropin measurement date, and interval between baseline and follow-up thyrotropin measurement date.

patients residing in iodine-deficient areas. Second, patients were required to have ≥2 TSH measurements to ascertain incident thyroid functional disease, and may thus have had a higher underlying likelihood of developing hyper- or hypothyroidism. Although this may limit generalizability, it is unlikely to have influenced internal validity given that this criterion non-differentially applied to cases and controls. Third, due to infrequent FT4/TT4 measurements, case and control status was ascribed according to TSH only, which may have led to outcome misclassification. However, restriction of thyroid functional testing to the ambulatory setting may have attenuated the risk of misclassification of non-thyroidal illness, and the prevalence of central thyroid functional disease is exceedingly low compared to primary thyroid disease.[24] Fourth, as with all observational studies, our findings do not prove that these associations are causal.

Conclusions

In conclusion, our findings indicate that ICM exposure is associated with incident hyperthyroidism and incident overt hypothyroidism in a broadly generalizable community-based population. Given the high prevalence of procedures employing ICM in contemporary medical practice and the adverse cardiovascular sequelae of thyroid functional disease, further studies are needed to determine the risk factors for iodine-induced thyroid functional disease, underlying mechanisms, and safe, cost-effective interventions that may reduce this risk.

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